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Nailfold videocapillaroscopy in patients with deficiency of adenosine deaminase 2 (DADA2): a case-control study

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Abstract

Background Deficiency of adenosine deaminase 2 (DADA2) is a rare monogenic autoinflammatory disease mainly characterized by the presence of systemic inflammation and vascular manifestations such as vasculitis and early-onset stroke. Raynaud's phenomenon (RP) can occur in up to 22% of DADA2 patients. The aim of this work was to investigate the microvascular status of DADA2 patients by the mean of nailfold videocapillaroscopy (NVC) comparing them with adequate healthy controls (HC) and primary RP patients.

Findings NVC data of 9 DADA2 patients (mean age 18 ± 6 y) followed at the Children Gaslini Institute were retrospectively retrieved and compared to age and sex cross matched 11 HCs and 7 with primary RP patients. The NVC parameters were classified according to the EULAR SG Fast Track Algorithm and distinguished between scleroderma-pattern (giant capillaries and/or loss of capillaries combined with abnormally shaped capillaries) and non-scleroderma patterns (non-specific NVC alterations). In all DADA2 patients, NVC showed the presence of non-specific alterations (capillaries with dilations in 100% of cases, abnormal shapes in 23% and microhaemorrhages in 11% of patients). The capillary density was normal and no scleroderma pattern was found. Between DADA2, RP patients and HC, no significant differences in the rate of each microvascular finding were detected (p values NS).

Conclusions This is the first report on NVC in DADA2 patients. Only non-specific abnormalities were found, characterized mainly by capillaries' dilations, but in the absence of giant capillaries. However, larger studies are needed to definitively disclose the microvascular status in DADA2 disease.

Keywords DADA2, Nailfold capillaroscopy, Vasculitis, Rare diseases

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Introduction

Deficiency of adenosine deaminase 2 (DADA2) is a rare monogenic autosomic recessive disease due to mutations of the *ADA2* gene [1, 2]. First discovered in 2014, DADA2 resembles polyarteritis nodosa (PAN), being characterized by the presence of systemic inflammation and vasculitis with ischemic manifestations resulting in early-onset strokes [1, 2]. Hypogammaglobulinemia and hematologic manifestations, ranging from monolinear cytopenia to bone marrow failure, have been described [3]. Only anti-TNF agents were found able to control the inflammatory symptoms and to prevent the ischemic/hemorrhagic strokes [4]. However, the hematologic alterations do not respond to anti-TNF and intravenous immunoglobulin replacement and in worst of cases bone marrow transplantation may be required.

Nailfold videocapillaroscopy (NVC) is a fast, reproducible, non-invasive technique for the direct study of the microvascular status, which is widely used for the assessment and description of peripheral microangiopathy in connective tissue diseases [5].

Since Raynaud's phenomenon (RP) can occur in up to 22% of patients [3], we aimed to investigate whether microvascular changes were present in children and adult DADA2 patients.

Findings

Methods

The clinical, NVC and genetic data of the DADA2 patients were retrospectively retrieved and compared to age-matched healthy controls (HC), and primary RP (pRP). The same trained physician (PFB) performed all NVC. A 200 × magnification optical probe connected to an image analysis software (Adamo S.r.l.- Horus) was employed. Two digital pictures of two-millimetre area in the middle of the nailfold bed of eight fingers, thumbs excluded, were collected for each subject [5].

The following capillaroscopic parameters were assessed: normal capillaries (diameter < 20 μm), capillary dilations (irregular or homogeneous increase of capillary diameter between 20 and 50 μm;), giant capillaries (homogeneously dilated normal shaped loops with a diameter ≥ 50 μm), microhaemorrhages, abnormal shapes (branched capillaries, sign of angiogenesis) and capillary number per linear mm (abnormal if capillary density < 7 capillaries/mm). The validated semiquantitative rating scale was adopted to score each of the five NVC parameters [5]. The mean absolute capillaries' count per linear millimetre (capillary density), was calculated with the same standardized methodology, considering all the 16 images collected for each subject [6].

The NVC parameters were classified according to the Fast Track Algorithm, and distinguished between scleroderma-pattern and non-scleroderma pattern [6].

All the patients signed a written informed consent to manage their clinical data collection/analysis, as a standard hospital procedure according to the rules of the University Hospital at the time of their first visit in our clinic. Ethical Committee approval was obtained for such studies (392REG2017).

Statistical analysis

Continuous variables were reported as mean value and standard deviation (SD) or median and interquartile range (IQR), when appropriate, categorical variables as count and percentage. Chi squared test or Kruskal–Wallis rank sum test was used to explore the heterogeneity of the characteristics by subject group. Fisher's exact test was employed when the chi-squared test assumptions were violated. The Mann–Whitney U test was used for comparing two independent groups when the continuous variables were not normally distributed. Spearman's rank correlation was used to calculate the relationship between ordinal variables, whereas Pearson's correlation analysis was used for metrically scaled variables. Any p values equal or lower than 0.05 were considered statistically significant. Datatab® Statistics Calculator was used for the statistical analysis.

Results

Nine patients with DADA2 were enrolled in the study and compared to 11 HC and to 7 pRP.

In Table 1 the characteristics of the DADA2 cohort are reported.

All DADA2 patients presented a low/absent enzymatic ADA2 activity. The patients were diagnosed according to genetic testing (Sanger sequencing or Next generation sequencing depending on the year of the diagnosis, in one case Whole genome sequencing was performed).

The disease onset was in infancy (mean age at disease onset 4.1 +/- 3.1 years, mean age at diagnosis 12.2 +/- 4 years) while the mean age at NVC was of 18.8 +/- 3 years. RP was present in 2 patients (22%), who presented also with digital ulcers, whereas livedo racemosa was present in 7 patients (78%), and ischemic stroke in 5 patients (55%). At the time the NVC was performed, all DADA2 patients were on treatment with etanercept (50 mg/week in adults, 0.8 mg/kg/week in children < 63 kg). The patients with pRP and HC did not present other particular manifestations.

In Table 2 the principal NVC characteristics of the cohort are reported.

In all DADA2 patients, NVC showed the presence of non-specific alterations: dilated capillaries in 100% of patients in the absence of giant capillaries, abnormal shapes (angiogenesis) in 11% and microhaemorrhages in 23%. Capillary density was normal (9.1 ± 0.3), and no scleroderma pattern was found. In the control group,

Table 1 Characteristics of the DADA2 cohort

Patient number	Age at disease onset (years)	Age at diagnosis (years)	Clinical manifestations	Previous treatments	Age ETN started (years)	Years of remission on ETN
1	1	5	Fever, livedo racemosa, subcutaneous nodules, stroke, dilative myocarditis, hypogammaglobulinemia	CS, anakinra, ASA	5	10
2	6	11	Fever, persistent systemic inflammation, recurrent MAS episodes, viral infections, genital ulcers, transient palpebral ptosis	NSAIDs GC, Anakinra, IVIG	13	5
3	5	16,5	Fever, livedo racemosa, ischemic stroke, hypertension, arthritis, arthralgias, abdominal pain, peripheral neuropathy	NSAIDs, MPD pulses, GC	16,5	6
4	1	20	Livedo racemosa, subcuteneous nodules, Raynaud's phenomenon, necrotic ulcers of extremities, ischemic stroke, diarrhoea, abdominal pain, colic ulcerations, hypogammaglobulinemia, recurrent infections of upper airways	NSAID, GC, Cyclophosphamide, MMF	20	10
5	7	18	Livedo racemosa, subcuteneous nodules, Raynaud's phenomenon, necrotic ulcers of extremities, sensorineural hypoacusia, peripheral neuropathy, diarrhoea, abdominal pain, arthralgia, hypogammaglobulinemia, hypertension related cardiomiopathy	NSAIDs, GC, MMF	18	10
6	1	12	Livedo racemosa, subcutaneous nodules, diarrhoea, recurrent upper airways infection	GC	12	10
7	9,5	9,5	Ischemic stroke, Anemia, systemic inflammation	GC	9,5	3
8	0,5	8	Fever, livedo racemosa, ischemic stroke, peripheral paresis of the VII cranial nerve, neurosensorial hearing loss, myocarditis	NSAIDs, CS	12	11
9	6	10	Fever, livedo racemosa, subcutaneous nodules, systemic inflammation		10	2

ASA Acetil Salycilic Acid, GC glucocorticoids, ETN etanercept, IVIG IntraVenous ImmunoGlobulins, MMF Mofetil Mycofenolate, MPD Methylprednisolone, NSAIDs Non steroidal Anti-Inflammatory Drugs,

Table 2 Principal nailfold videocapillaroscopic characteristics of the whole cohort

	DADA2 *N* = 9	pRP *N* = 7	HC *N* = 11
Sex, F (%)	6 (66%)	6 (85%)	5 (45%)
Age at NVC, mean ± SD	18 ± 6 y	16 ± 3 y	17 ± 3 y
Mean capillary density (median)	9	9	9
Dilations 0–33%, n(%)	7 (78)	3 (48)	6 (54)
Dilations 33–66%, n(%)	2 (2)	4 (57)	2 (18)
microHaemorrages (0–33%), n(%)	2 (23)	0 (0)	1 (9)
Abnormal shapes 0–33%, n(%)	1 (11)	1 (14)	4 (37)
Capillary reduction 0–33%, n(%)	0 (0)	0 (0)	2 (18)

DADA2 Deficiency of adenosine deaminase 2, pRP primary Raynaud's Phenomenon, HC Healthy Controls. P-value not significant in the comparison between the three groups. Frequencies were compared in pairs between groups (DADA2 vs. pRP and DADA2 vs. healthy controls). Pairwise comparisons were performed using the Chi-square test. In cases where the expected frequencies were too low (including instances with zero values), Fisher's exact test was applied

72% of HC and 100% of pRP displayed capillary dilations in the absence of giant capillaries, whereas abnormal shapes were found in 37% and 14% of HC and pRP respectively. Microhemorrhages were found in 1 HC while were absent in pRP. No significant differences in the rates of each microvascular finding were detected between DADA2, pRP patients and HCs (all p values NS, Table 2). Subgroup analysis based upon clinical phenotype was not performed due to the low sample size.

Discussion

This is the first report about NVC findings in DADA2 patients. In our cohort, non-specific NVC alterations, especially dilated capillaries, were found in all 9 DADA2 patients, even if no significant differences were found when compared to patients with pRP and healthy controls.

Since in presence of vasculitis the active involvement of vessels including capillaries should be expected, NVC analysis could potentially represent an important tool of investigation.

In the literature there are only few uncontrolled studies regarding NVC and vasculitis, reporting non-specific NVC changes, and detected by different methods [7].

Bertolazzi et al. reviewed the literature on NVC features of IgA vasculitis (IgAV), Kawasaki disease, Behçet's syndrome (BS), Granulomatosis with PolyAngiitis (GPA), thromboangiitis obliterans, and cryoglobulinemic vasculitis, reporting heterogeneous minor or nonspecific NVC changes [7]. Sendino Revuelta et al. described the NVC features of 15 patients with ANCA-associated vasculitis (AAV), giant cell arteritis and PAN (2 patients). The findings were non-specific, constituted mainly by microhemorrhages (70%), concluding for a limited role of NVC in vasculitis [8]. On the contrary, Anders et al. reported the presence of avascular areas in 90% of their patients

with GPA [9], while in IgAV, tortuosity, oedema, and architectural derangement were described in a series of 31 patients [10], and in children a correlation between disease activity and NVC changes was reported [11]. In BS, a correlation was found between enlarged capillaries and a younger age at disease onset, hypertension, and superficial phlebitis [12]. In a literature review regarding AAV, non-specific NVC abnormalities were reported in 70–80% of patients, highlighting a different pattern between non-active and active patients, the latter group presenting a higher rate of abnormalities when compared to healthy subjects and inactive patients [13]. Keret et al. recently evaluated 25 active and inactive vasculitis patients (11 PAN, 7 AAV, 2 Takayasu, 1cryoglobulinemia, 3 Sjogren, 1 primary central nervous system vasculitis, 1 systemic lupus erythematosus), comparing them to HC, demonstrating frequent capillary abnormalities, with higher rates of neoangiogenesis, microhemorrhages and capillary loss in patients with active disease, and described two novel NVC abnormalities: "rolling" (slow capillary flow) and "peri-capillary stippling" (PCS), small deposits that may represent capillary leak. This latter finding was absent in all HC and was found in 14% of RP (64% diagnosed with scleroderma or a related disorder) [14].

DADA2 can present with livedo racemosa, strokes and with a microvascular involvement resulting in RP or digital ulcers, thus resembling PAN [2]. In the literature, few reports address NVC findings in PAN (Sendino-revuelta et al. 2 patients, Keret et al. 11 patients), with mainly non-specific changes reported [8, 14]. However, Keret et al. reported a significant difference between active and inactive cases [14], and Bernardino et al. reported a possible normal NVC in PAN patients without RP, while in its presence a reduced capillary density, microhemorrhages, and edema were found, describing edema, capillary flow sludge, and multiple hemorrhages in case of digital ischemia [15].

In our cases, the DADA2 capillaroscopic changes were non-specific (mainly capillary dilations) and no differences were found in comparison to HC and pRP. Moreover, among DADA2 patients no difference was found between those with and without pRP.

In this context, the lack of any specific capillaroscopic findings could be also due to the fact that all the patients were on treatment or had inactive disease. In addition, the transition of NVC patterns during disease progression has been reported in immune-mediated diseases like connective tissue diseases. This should be considered possible in all pathological conditions causing microvascular damages, including DADA2.

The major limitation of the study consists in the small number of included patients (DADA2 is a rare monogenic disease).

In conclusion, this is the first report that investigates the NVC findings of DADA2 patients. At the moment, the actual data suggest that DADA2 patients on treatment do not present specific microvascular modifications. However, larger studies on treatment *naïve* patients are needed do definitively disclose the real conditions of the microvascular status in DADA2 disease.

Abbreviations

AAV	ANCA-associated vasculitis
BS	Behçet's Syndrome
DADA2	Deficiency of adenosine deaminase 2
GPA	Granulomatosis with PolyAngiitis
IgAV	IgA vasculitis
NVC	Nailfold videocapillaroscopy
PAN	Polyarteritis nodosa
pRP	Primary Raynaud's phenomenon
RP	Raynaud's phenomenon

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All authors reviewed the results and approved the final version of the manuscript.

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Data availability
Data are available upon reasonable request.

Declarations

Ethics approval and consent to participate
The local Ethical Committee approval was obtained for this study (392REG2017).

Consent for publication
The included patients have given their consent to publication.

Competing interests
None declared.

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